DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Edward John Allera
Donald E. Segal
Akin, Gump, Strauss, Hauer & Feld, L.L.P.
1333 New Hampshire Avenue, N.W.
Suite 400
Washington, D.C. 20036

Re: Docket No. 99P-5109/PSA1

Dear Messrs. Allera and Segal:

This responds to your petition, dated November 29, 1999, filed on behalf of R & D Laboratories (R & D), to stay acceptance and filing of any new drug application (NDA) for ferric hydroxy saccharate complex. In that petition, you raise a number of concerns regarding actions we have taken that you believe violate marketing exclusivity granted to the drug Ferrlecit, sponsored by R & D. Because your petition relates to a drug product that is not approved, there are limitations on the information we can disclose. However, this response is intended to provide you with the maximum reassurance possible that (1) we are aware of your client's scientific and legal concerns, and (2) we are thoroughly and carefully considering these issues in applying the marketing exclusivity granted to Ferrlecit.

You document that R & D holds approved new drug application (NDA) 20-955 for Ferrlecit (sodium ferric gluconate complex in sucrose injection), which was granted 5 years of new chemical entity exclusivity under sections 505(c)(3)(D)(ii) and (j)(5)(D)(ii) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR 314.108. Exclusivity for Ferrlecit began on the date of approval, February 18, 1999, and will end on February 18, 2004.

You believe that American Regent Laboratories, Inc. (ARL) has pending before us an NDA that, if filed by us under 21 CFR 314.101, will violate the exclusivity granted to R & D for Ferrlecit. You correctly state that a grant of new chemical entity exclusivity generally bars the submission of any abbreviated new drug application (ANDA) or application described in section 505(b)(2) of the Act for a drug containing the same active moiety for a period of 5 years.[1] New chemical entity exclusivity does not bar submission and review of a "stand alone" 505(b)(1) NDA during the 5-year period, nor does it bar submission and review of an NDA for a drug that does not contain the same active moiety.

[1] An ANDA or 505(b)(2) application may be submitted at the end of 4 years if the application contains a certification that a patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" for the innovator drug product is invalid, unenforceable, or will not be infringed. There are no patents listed for Ferrlecit.

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You document that ARL has made public the fact that it has an NDA for iron sucrose injection pending. In light of such disclosures, FDA has obtained permission from Luitpold Pharmaceuticals, Inc. (Luitpold), ARL's parent company, to disclose certain additional facts regarding the NDA that you reference.

FDA has filed an NDA submitted by Luitpold for Venofer (iron sucrose injection). This filing of an NDA for iron sucrose injection during the period of R & D's exclusivity is permissible in either of two circumstances. The first is if we determine that the iron sucrose drug product does not contain the same active moiety as Ferrlecit.[2] At the time an NDA is submitted to us, an initial analysis of the chemical composition of the drug's active ingredient and what is known about its pharmacological action is done as part of the investigational new drug/NDA classification system. This analysis may be reassessed during the NDA review process as our staff becomes more familiar with the drug. Luitpold has not disclosed publicly any determination made by us as to whether Ferrlecit and Venofer (iron sucrose injection) have the same active moiety, and therefore we cannot disclose such information. In the second circumstance, if it is determined that the two drugs had the same active moiety, we can file and review the Venofer application only if it is not an ANDA or a 505(b)(2) application.

The Venofer NDA submitted by Luitpold is not a 505(b)(2) application or an ANDA. It is a "stand alone" NDA as described in section 505(b)(1) of the Act, and thus can be filed, reviewed, and approved even if Venofer has the same active moiety as Ferrlecit. The Venofer NDA was filed as a "stand alone" 505(b)(1) application because FDA made a threshold determination that the studies which Luitpold has conducted or to which it has a right of reference are sufficient to support a substantive review of the application.

All NDAs are required to contain substantial evidence of effectiveness, consisting of data from adequate and well-controlled studies. They are also required to contain data showing the drug proposed is safe for use under the conditions described in the labeling. As explained in our guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), data establishing effectiveness can be derived from numerous sources and from different types of studies. Luitpold submitted clinical studies using baseline controls to demonstrate the safety and effectiveness of Venofer. Under 21 CFR 314.126, studies with historical controls are recognized as being capable of demonstrating that a drug is effective. The draft guidance prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *E10 Choice of Control Group in Clinical Trials* provides additional information on the use of historical controls and states that base line controls are a type of historical control (64 FR

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[2] "Active moiety" is defined at 21 CFR 314.108(a) as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."

51767).[3] FDA made a threshold determination that Luitpold conducted, or had right of reference to, studies sufficient to permit a substantive review of the application. Specifically, Luitpold did not refer to, or in any other way rely on, data from the "Colorado" study (petition at 9) submitted in the Ferrlecit NDA. In our review of the Venofer NDA, we are not relying on the "Colorado" data or reports of any other investigations that Luitpold did not conduct or to which it does not have right of reference.

For additional information regarding our interpretation and application of section 505(b)(2) of the Act, please consult the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (enclosed) and the August 26, 1998, response to a petition for stay of action filed on behalf of Meretek*diagnostic*, Inc. (Docket No. 98P-0167/PSA1 (enclosed)). These documents describe some of the characteristics of a 505(b)(2) application, particularly what types of information may make an NDA a 505(b)(2) application and what information does not make an NDA a 505(b)(2) application.

For the reasons given above, your petition for stay of action is denied.

Sincerely yours,

for Dennis Baker
Associate Commissioner for
Regulatory Affairs

Enclosures

[3] The two draft guidances mentioned in this letter do not have any regulatory effect. However, they are useful as references reflecting current FDA thinking or, in the case of the ICH draft guidance, the thinking of experts from around the world.